The NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) User's Guide

https://biolincc.nhlbi.nih.gov

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1.0 ABOUT BIOLINCC

The National Heart, Lung and Blood Institute (NHLBI) Biologic Specimen and Data Repository is the coming together of two entities: the NHLBI Biologic Specimen Repository (NHLBI Biorepository), managed by the NHLBI, Division of Blood Diseases and Resources (DBDR), Transfusion Medicine and Cellular Therapeutics Branch, and the NHLBI Data Repository, managed by the NHLBI, Division of Cardiovascular Sciences (DCVS), Epidemiology Branch. These two programs have always had a similar mission, namely to enhance and facilitate further research in cardiovascular, pulmonary and hematologic conditions by providing access to qualified investigators to stored biospecimen and data collections.

The mission of BioLINCC is to facilitate access to, and maximize the scientific value of, the Biorepository and Data Repository and promote the availability and use of other NHLBI funded population-based biospecimen and data resources.

This website serves to coordinate searches across data and biospecimen collections and to provide an electronic means for requests for additional information and the submission of requests for collections. Researchers wishing to apply to submit biospecimen collections to the NHLBI Biorepository for sharing with qualified investigators may also use this website to initiate that process.

2.0 THE BIOLINCC WEBSITE: STRUCTURE AND FUNCTION

2.1 OVERVIEW

The BioLINCC website is accessed at https://biolincc.nhlbi.nih.gov/.

This website is the primary interface with the NHLBI Biologic Specimen and Data Repositories Information Coordinating Center (BioLINCC). The system is comprised of two levels: public information which is available to all users, and a private workspace which is available to registered users.

The public website provides a wealth of information on historical NHLBI clinical and epidemiologic studies which have data or biospecimens in the NHLBI repositories, and includes study summaries, references, and study operational documents. This information is provided in the form of searchable study description pages. A more in-depth search function of all material archived on the website is also available. Additional resources include links to information on the preparation of study datasets which are suitable for use as shared resources, BioLINCC forms and templates, and a news feed of recent additions and updates to the posted collections.

Registration (see section 2.3.2) is required to request resources from the NHLBI Biologic and Data Repositories. Once a request has been submitted, communications and document transmissions between the researcher and BioLINCC are handled electronically through the secure website request interface.

2.2 DEFINITIONS

See also the online glossary.

- **BioLINCC Staff** – Personnel at the contractor level responsible for the maintenance of the BioLINCC website and processing of requests.
- **NHLBI Staff –** NHLBI personnel responsible for the administrative and scientific oversight of BioLINCC.
- **Biorepository Staff** – Personnel at the contractor level that store, process, and maintain physical biospecimens from BioLINCC collections.
- **Parent Study –** The clinical study collecting the data and/or biospecimens. The principal or primary study.
- **Study Collection** – A particular clinical trial or longitudinal/observational study that has been funded by NHLBI and which has submitted materials to BioLINCC.
- **Study Datasets** – A collection of the clinical data that encompass the primary outcomes of a study.
- **Biospecimens** – A quantity of tissue, blood, urine, or other biologically derived material. The NHLBI Biologic Specimen Repository stores human biospecimens.
- **Biospecimen Characterization Data** – The quantitative or qualitative information linked to the biospecimen which may include: type of biospecimen (i.e. plasma, urine), type of fixative or additives, some demographic data, and laboratory test results.
- **Requestor** – The user who submits a request to the BioLINCC website. All requests must be submitted by a PI/Senior Researcher who:
    - Is a permanent employee of their institution at a level equivalent to, at a minimum, a tenure-track professor or senior researcher. This does not include lab technicians or trainees, e.g. post-docs or graduate students.
    - Has oversight responsibility for others named on the data access research request who will be granted access to the data.
    - Is accountable for ensuring that all aspects of data usage align with the terms of the Research Materials Distribution Agreement and institutional policy.
    - Resides in the same country as their institution.
- **Principal Investigator (PI)** – The person responsible for oversight of a project involving materials requested from BioLINCC. This person must be named in the IRB documentation for the proposed project and sign the Research Materials Distribution Agreement prior to access to BioLINCC biospecimens and/or data. The requestor is generally the PI and leads the analysis.

- **Institutional Review Board (IRB)** – A body that provides complete and adequate review of human research and its institutional, legal, scientific, and social implications. When referred to in the context of the BioLINCC, this is the body overseeing the research proposed by the requestor. It may be affiliated with the requestor's institution or may be an independent body only if the requestor's institution does not have an internal IRB. IRBs may grant approval of the research or determine that it does not involve human subjects, i.e. is not regulated. Equivalent international bodies (e.g. Ethics Committees) are also recognized by the NHLBI.

- **Approved Request Users** – Additional registered users from the PI's institution that may be added to the request after submission (see section 3.2.5) for the purposes of updating the request and inclusion on request communications.

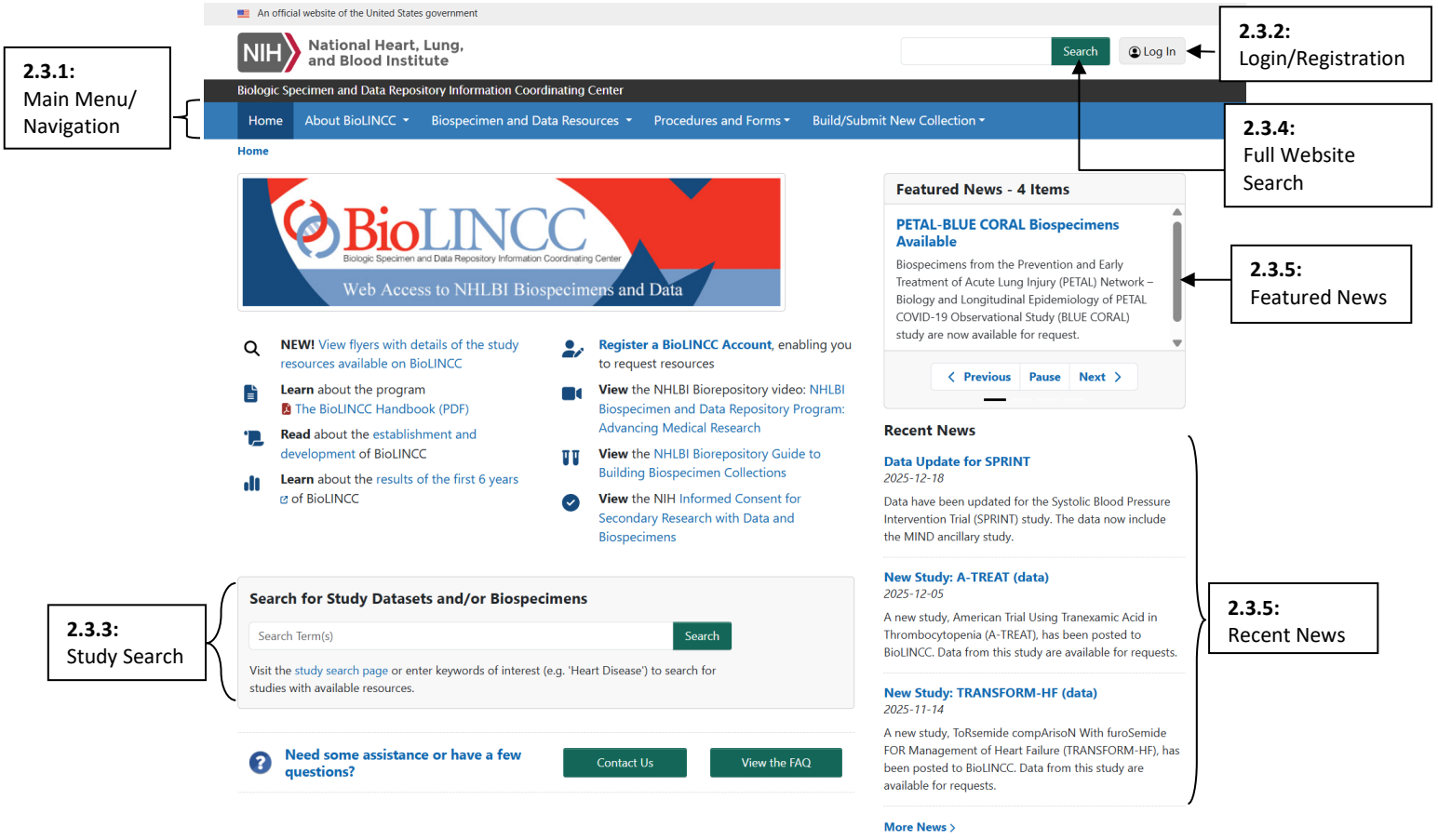
- **Research Materials Distribution Agreement (RMDA)** – A standardized legal agreement that must be completed prior to the distribution of BioLINCC materials, namely data and/or biospecimens. Applicable parties to the agreement include the PI requesting BioLINCC materials, the investigator's institution that will act as recipient of the materials, and the NHLBI as custodian of the materials.

- **Other Authorized Users** – Staff at the PI's institution that will work with BioLINCC materials. In the case of biospecimens, this may include users outside of the institution who are under a contractual non-disclosure agreement such that the biospecimens remain within the purview of the PI at the recipient institution, i.e. testing labs.

- **Authorized Institutional Business Official (AIBO)** – An individual who is authorized to enter into a contract on behalf of the recipient institution.

2.3 THE BIOLINCC HOME PAGE – PUBLIC INFORMATION

FIGURE 2.3: THE BIOLINCC HOME PAGE



2.3.1 MAIN MENU

The navigation bar at the top of any BioLINCC page provides access to the various sections of the website including the **Home** page, **About BioLINCC, Biospecimen and Data Resources**, **Procedures and Forms**, and **Build/Submit New Collection.**

The **About BioLINCC** section contains high-level information about the BioLINCC program, including Frequently Asked Questions (FAQs); a Contact Us page where users may submit questions not answered in the FAQs or comments via an online form, email, or through the other contact means listed; and a glossary of commonly used terms.

The **Biospecimen and Data Resources** section contains information about BioLINCC and Non-BioLINCC resources. **Overview** provides a brief description of the resources listed on the website. Like the Home page, visitors can search **Studies** that are available for request using search term(s) or one of the available filters. Visitors can explore the **Teaching Datasets** which have been developed as educational tools or the **Public Use Datasets** which are freely available

datasets for research purposes. Researchers with an existing NHLBI BioLINCC data set use agreement which is expiring may submit a request to **Renew an Existing Data Use Agreement**. This section also provides links to information about **Publications** stemming from BioLINCC resources and to **Funding Opportunities** that may be applicable to research using BioLINCC resources. An index is provided for select **Non-BioLINCC Resources**; these are not maintained by BioLINCC but are available for request though external sites. A link to NHLBI **COVID-19 Resources** and FAQs is also included.

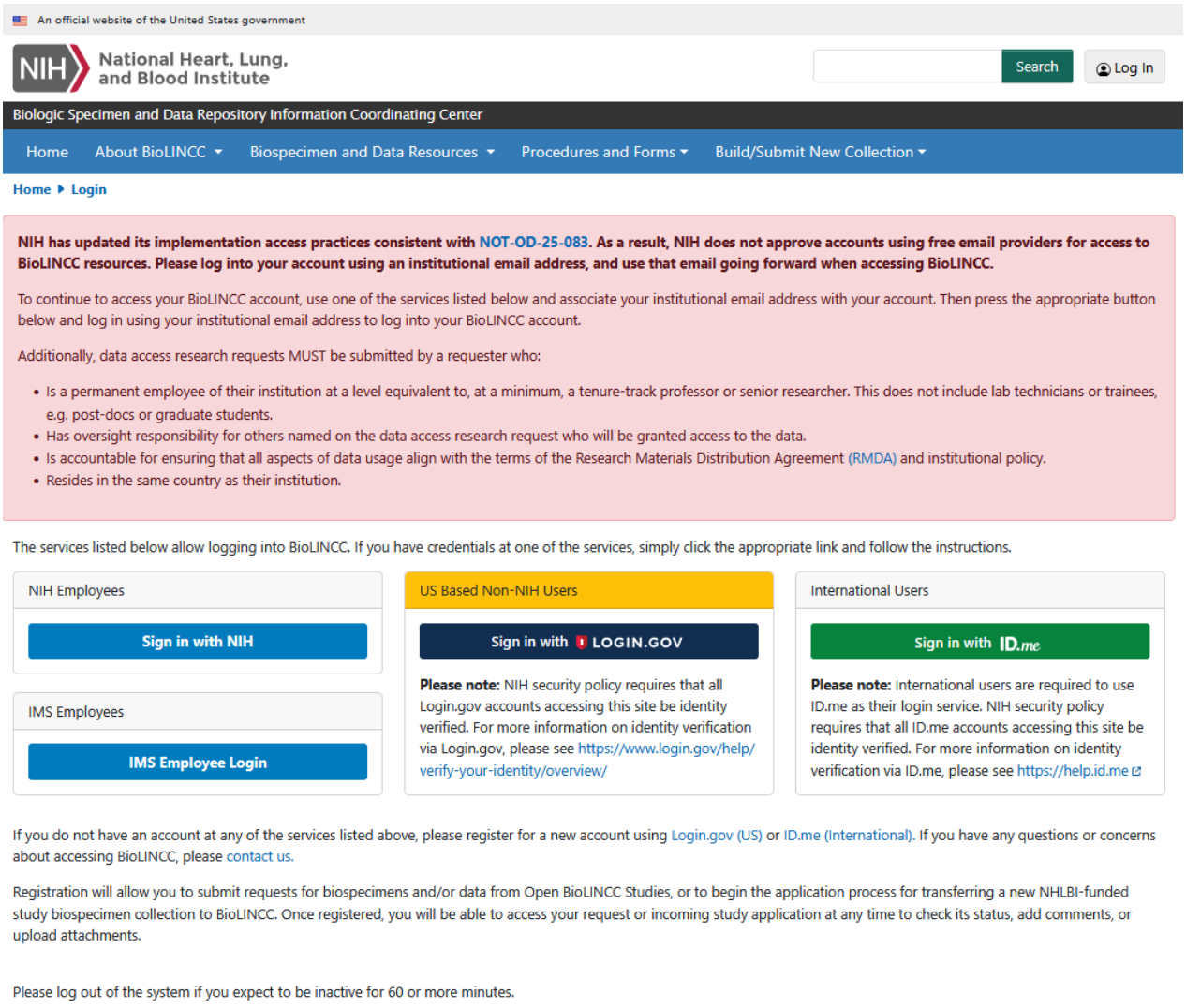
The **Procedures and Forms** section includes links to **Form Templates** for each request type and the Incoming Biospecimen Collection Questionnaire, as well as **Agreement Templates** including the Research Materials Distribution Agreement (RMDA) and Collaborator Attestation form used for biospecimen and/or data requests, and Material Transfer Agreement (MTA) for the incoming biospecimen collection process.

The **Build/Submit New Collection** section is primarily for Parent Study researchers of NHLBI funded studies who are preparing to **Submit Datasets** or **Submit Biospecimens and Datasets** for use as shared resources. Included in this section are downloadable documents entitled “The NHLBI Biorepository Guide to Building Biospecimen Collections for Study and Future Research Use” and “Informed Consent for Secondary Research with Data and Biospecimens”, a short video highlighting the benefits of creating a quality biospecimen collection to serve as a valuable research resource.

2.3.2 LOGIN/REGISTRATION

Visitors wishing to request biospecimen or data resources, renew an existing data set agreement or register to submit a new biospecimen collection must become registered users to access these private workspaces. The login and account registration links are located on the upper right part of the page.

FIGURE 2.3.2: THE BIOLINCC LOGIN/REGISTRATION PAGE



NIH Staff can login using their existing credentials by clicking the "NIH Login" button. When logging in for the first time via this method, users will be asked for some additional details.

Non-NIH Staff should register via the Login.gov or ID.me options. Users with a U.S. state-issued ID should use Login.gov. International users are required to use ID.me as their login service. On-screen prompts will guide the user through registration. Documentation verifying your identity and email confirmation is required to create an account in accordance with Identity Assurance Level 2 (IAL2) standards. For more information on identity verification via Login.gov, please see https://www.login.gov/help/verify-your-identity/overview/. For more information on identity verification via ID.me, please see https://help.id.me.

As a result of access practices consistent with NOT-OD-25-159, NIH does not approve accounts using free email providers (Gmail, Yahoo, etc.) for access to BioLINCC resources. Therefore, users

must create an account using an institutional email address and use that email when accessing BioLINCC.

Users with a BioLINCC account that predates the Login.gov and ID.me login options must still create an account through one of these services, which will be linked to your existing BioLINCC profile if your email address used to login matches the existing profile. For assistance with updating the email address on your legacy profile, please contact BioLINCC.

Only BioLINCC staff may use the "IMS Employee Login" option.

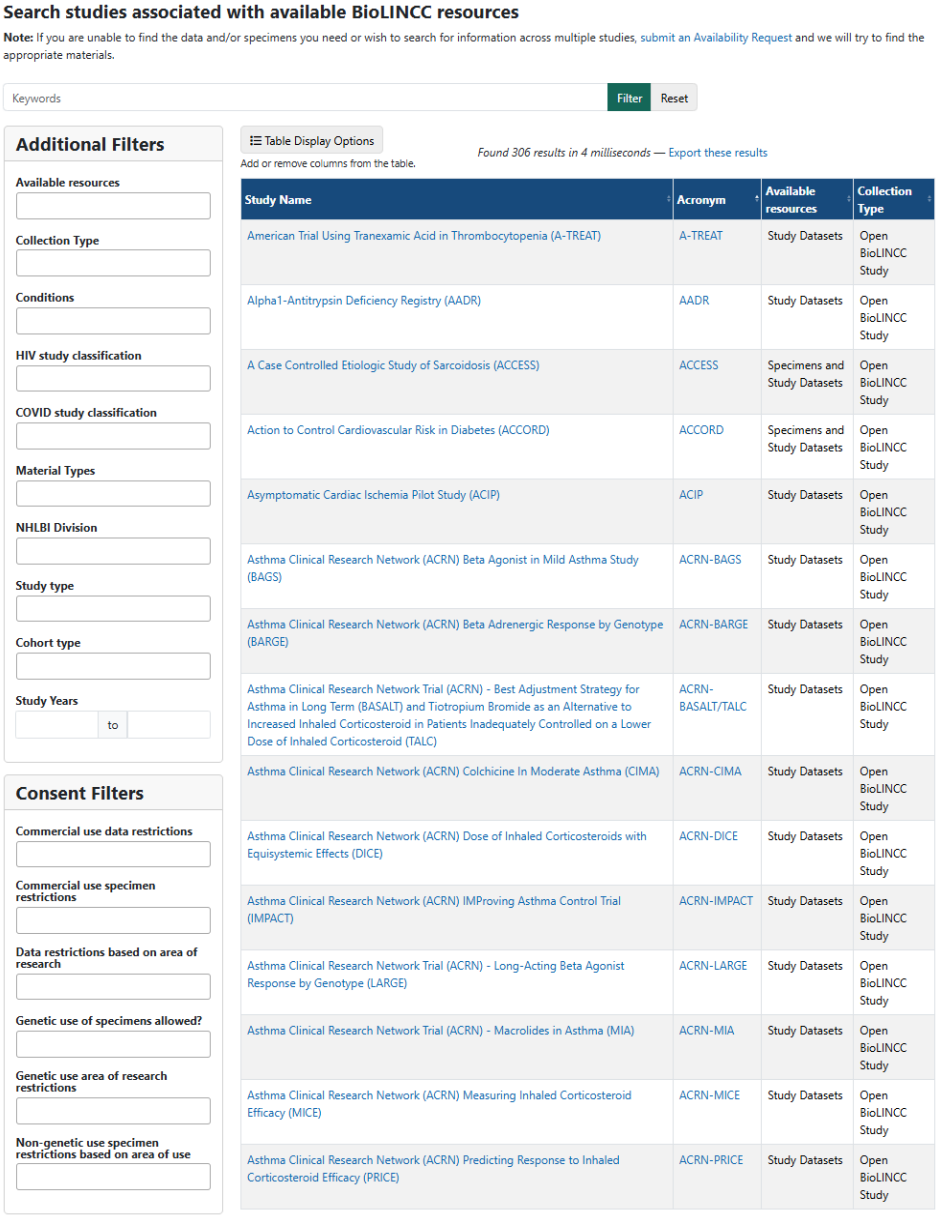
Users that have an established account linked to one of the login services may update their email address by adding their new institutional email address to their respective login service account (Login.gov or ID.me) and then use that email to sign into BioLINCC. This will update the email address used for the user's BioLINCC profile.

Once logged in as a registered user, a section called **My BioLINCC** appears on the navigation bar and allows users to view their saved and submitted requests and to access request-specific communications.

2.3.3 STUDY SEARCH

The study search utility, located on the BioLINCC home page and on the Studies page, provides a way to filter the study resources that are displayed, based upon parameters selected via the tabs and drop-down selections and/or key words provided by the user. This search utility provides results based upon collection type (data, biospecimens or both), biospecimen material type, keywords as drawn from the NIH Clinical Trials summary, and other main study properties. User-supplied text for searching is matched against the contents of each study web page. Associated study documents are not searched using this utility (but see section 2.2.4, Full Website Search).

FIGURE 2.3.3: STUDY SEARCH



2.3.4 FULL WEBSITE SEARCH

The full website search, located in the upper right corner of any BioLINCC page, provides an interface for more detailed searches across the full searchable contents of the BioLINCC website. This search is more powerful than the study webpage search, and offers advanced search capabilities. Because of the volume of associated documents posted on the BioLINCC site, this search may return a very large number of hits depending on the specificity of the search terms used. It is most useful as a secondary tool to search for studies which may have examined or collected very specialized types of data.

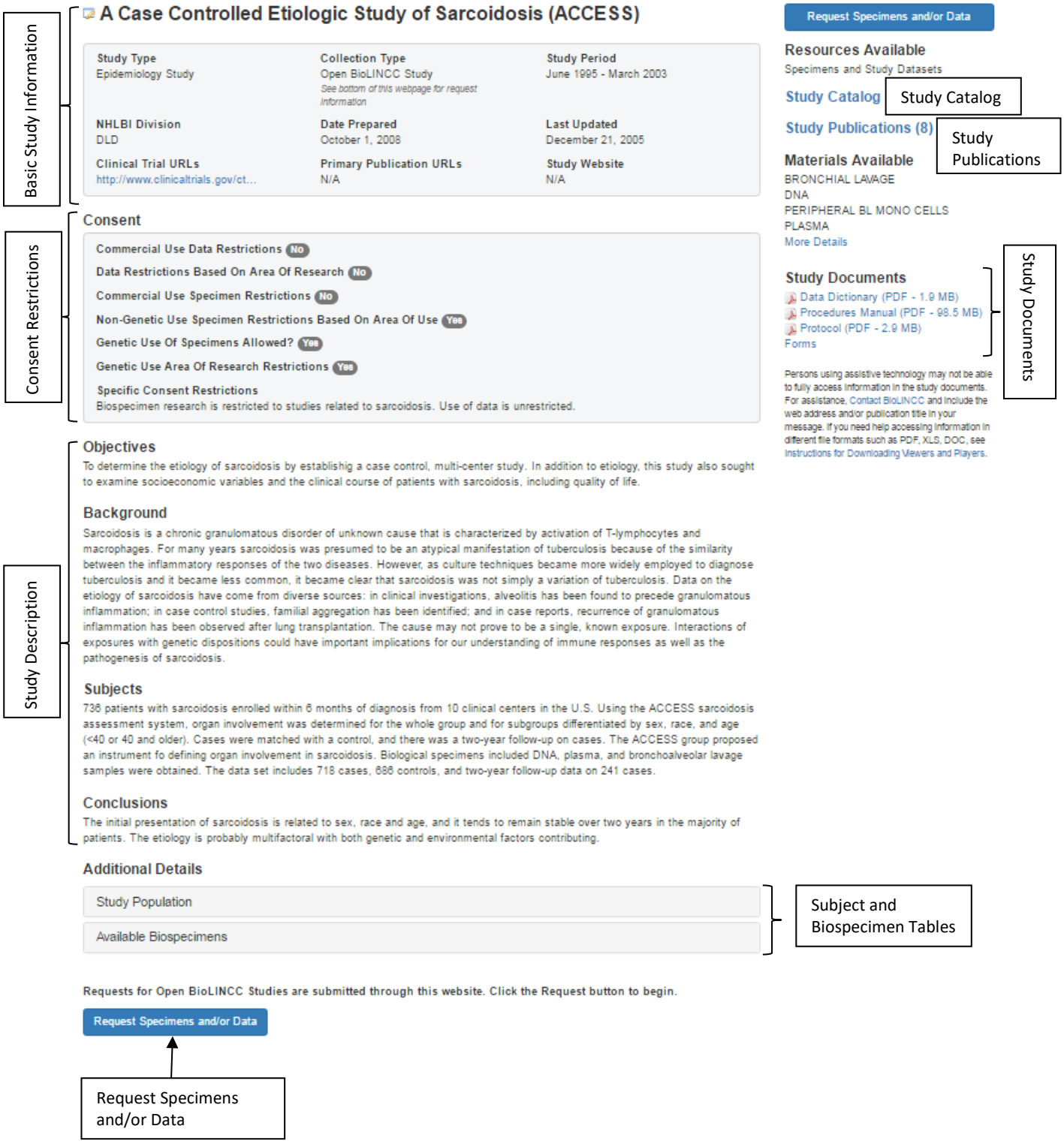
2.3.5 FEATURED AND RECENT NEWS

News items are posted to announce the availability of new studies or study updates, and to provide notifications of special events and funding opportunities. If there is more than one featured news item, each item will cycle through the display carousel automatically, or manually using the “previous” and “next” buttons. Recent news items are displayed below any featured news items with a link at the bottom of the section to view older news items.

2.4 STUDY DESCRIPTION PAGE

Each study with resources available on BioLINCC has a description page, which can be accessed from the Studies page. Figure 2.4 illustrates the typical layout of a study page where data and biospecimens are available. BioLINCC users may also initiate a request for available resources from this page.

FIGURE 2.4: EXAMPLE STUDY DESCRIPTION PAGE



- **Basic Study Information**: Lists high level information about the study including study title, type, period, Clinical Trial URL(s), and study website (if available).
- **Study Description:** This provides an overview of the rationale, methodology, and findings of the study as originally conducted.
- **Consent Restrictions:** This box displays whether there are any restrictions for the type of research that may be conducted using the data and/or biospecimens. In some cases, restrictions may make a request ineligible for fulfillment. In the example shown in Figure 2.4, biospecimens from the ACCESS collection may be used only for sarcoidosis-related research, and therefore requests for use of biospecimens in other areas of research would be denied. In other cases, materials from only the subset of subjects who consented to the proposed research type would be provided. For example, for studies with commercial use data restrictions, investigators requesting data for commercial use would be eligible to receive only the subset of the overall dataset that was provided by subjects who consented to commercial research.
- **Additional Details:** These sections at the bottom of the description are available for studies linked to biospecimens in the Biorepository. They can each be expanded to view more detailed information regarding the study subjects and biospecimens included in the collection. The Study Population tables provide information regarding the number of study participants by age, sex, race, and treatment arm who are included in the study data. Some collections from transfusion-related studies have a limited set of data (referred to as "characterization data"); for these studies, tables display the available biospecimens for subjects by study visit and material type. These numbers are regularly updated and are provided to help interested investigators get a sense of whether the collection may have sufficient materials for the proposed research. Specific biospecimen availability will be provided by BioLINCC staff during the request process in accordance with the requestor's subject and biospecimen criteria (see section 3.4) and availability is subject to review by the NHLBI, BioLINCC, and the NHLBI Biorepository.
- **Study Catalog:** This is available for studies with biospecimens, and provides an alternative format for viewing key study information. Publicly available sections include the Basic Study Information, Study Consent, Additional Study Information, Study Population (where applicable), and Available Biospecimens.
- **Study Publications:** This will link the user to the database of publications associated with available BioLINCC resources, subset by the particular study being viewed. This is not an exhaustive list of publications, but can provide users with more information on the types of published research that have been conducted using BioLINCC data and/or biospecimens.
- **Study Documents:** These are a key source of information for understanding the study and available data. The Data Dictionary is a standard file generated by BioLINCC that includes a listing of all dataset variables available in the study data package. Users can search this file, potentially in conjunction with study forms which may be annotated with the variable names, to determine whether the data required for a project is included prior to submitting a request. Studies with only biospecimens available may still have a

data dictionary that includes biospecimen characterization data. Other posted study documents will vary, but typically include a protocol and/or manual of procedures, forms, and other essential documents.

2.5 MY BIOLINCC – THE PRIVATE WORKSPACE AREA

Registered BioLINCC users gain access to the private workspace area for request submission and processing. Resource request types include BioLINCC Studies, Teaching Datasets, Public Use Datasets, and Data Renewal Requests (for expiring existing data agreements). Registrations and processing functions for applications to submit new biospecimen collections are also included in the private workspace area. Upon registration, an additional menu item, My BioLINCC, appears as an option in the Main Menu. Selecting My BioLINCC brings up a new screen which contains tabbed links to the user's submitted requests and to requests which have been saved but not yet submitted for processing. From these listings the user may bring up the information and access features from each request (see section 3.2). Registered users only have access to requests that they have initiated, unless the requestor adds other approved users to the request (see section 3.2.5).

3.0 REQUESTING BIOSPECIMENS AND DATA

3.1 OVERVIEW

The BioLINCC website at https://biolincc.nhlbi.nih.gov/ is the interface for all applications for biospecimens and data stored in the NHLBI Biologic Specimen Repository (Biorepository) and the NHLBI Data Repository. There are three types of applications:

1. Biospecimens and vial characterization data (no associated research dataset available)
2. Research datasets
3. Biospecimens and associated research datasets

The request forms vary between the request types and are not interchangeable.

The request timing varies significantly, and often is dependent on how quickly the requestor is able to provide the required documentation or respond to questions from BioLINCC staff. Data requests may be completed in as little as one week. Requests that include biospecimens require additional time for evaluation of the biospecimen inventory and suitability, formal reviews of the request, biospecimen preparation and your position in the request queue. We typically advise that investigators allow at a minimum three to six months for completion of a biospecimen request, assuming that funds are immediately available and all request requirements are met in a timely manner. Requests that are inactive while pending requestor documentation or information will be administratively closed.

Biospecimens and datasets are provided free of charge to qualified investigators, with the exception of the cost of shipping biospecimens to the testing facility. Biospecimens are only made available if funds are available to perform the research.

Table 3.1 summarizes the supporting documentation requirements for each application type.

TABLE 3.1: DOCUMENTATION REQUIRED BASED ON APPLICATION TYPE

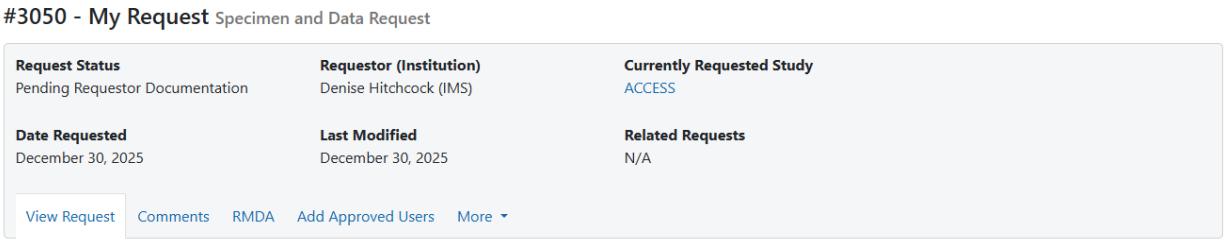
Supporting Documentation Requirement	Biospecimens and vial characterization data	Research dataset	Biospecimens and associated research dataset
Summary of research plan (protocol)	Required		
IRB review (from applicant's institution)	Written approval from the requestor's IRB must be submitted stating that the IRB has either a) performed a review of the project and issues an approval, or b) declared that the research project is exempt from review.	For the majority of studies, written approval from the requestor's IRB must be submitted stating that the IRB has either a) performed a review of the project and issues an approval, or b) declared that the research project is exempt from review. A few studies require full or expedited review and an exemption statement cannot be accepted. This requirement is noted on the Study Page.	
PI Curriculum Vitae	Required	Optional	Required
Funding Documentation	Required	Optional	Required
Online request form	Required		
Collaborator Attestation form	Required; template available on BioLINCC website		
Research Materials Distribution Agreement (RMDA)	Required; components are generated by the website automatically		

All requests undergo a review process that includes the qualifications of the researcher, availability and appropriateness of the biospecimens/data for the proposed research, and compliance with human subject regulations. Section 3.3.4 describes the review of data requests and Section 3.4.6 the review of biospecimen requests.

3.2 REQUEST FEATURES

Upon submission of any request, the requestor receives an automatic email confirmation of the submission, including a direct link to the request comment page as well as information on the next steps. Requestors, any approved request users (see section 3.2.5), and BioLINCC staff also receive notification emails when the request or comment pages are updated; these emails also contain direct links back to the specific request workspace.

FIGURE 3.2 REQUEST HEADER AND TABS



3.2.1 REQUEST HEADER

This displays high level information about the request including request status, requestor, requestor institution, currently requested study/studies, the date the request was submitted, and the date the request was last modified.

3.2.2 VIEW REQUEST TAB

Provides a view of the submitted request form and attachments. An in-process request may be modified using the “Edit Request Form” icon at the top of the page. BioLINCC staff will be notified of any changes to the request form and such changes may require additional review.

3.2.3 COMMENTS TAB

The main communication medium between the requestor, approved request users, and BioLINCC staff. The comments page is a cumulative and time-stamped record of the request discussion. Documentation attachments may also be submitted on this page.

3.2.4 RMDA TAB

This tab is only accessible after a request has been formalized. This tab is where the requestor will provide the information necessary for BioLINCC to generate the Research Materials Distribution Agreement. The initial and fully executed copies of the agreement will also be posted here.

3.2.5 ADD APPROVED USERS TAB

The requestor may search for and add additional users from their institution that are registered with BioLINCC to the request. Additional users may update the request and will be included in email notifications.

3.2.6 MORE

The ability to create a printable PDF of the submitted request, or to review and approve the findings of a BioLINCC biospecimen search, may be accessed via the More drop-down menu.

3.3 STEPS FOR REQUESTING DATA

Requests are made through the BioLINCC website at https://biolincc.nhlbi.nih.gov/.

3.3.1 SEARCH AND REGISTER

The researcher may use the BioLINCC website keyword and search functions (see sections 2.3.3 and 2.3.4) to identify a study or studies which may have suitable resources for the proposed research. Alternatively, the researcher may proceed directly to the target study page if already known. At the bottom and right-hand side of the Study Description Page (see section 2.4) is a Request button. The researcher must be logged in as a registered user on the BioLINCC site to submit a request; if not logged in, clicking on this button will open a prompt for login or registration (see section 2.3.2).

The requestor should review the Data Dictionary posted to each Study Description Page to verify that the data elements of interest are available for request. BioLINCC provides a standard data package upon fulfillment of a request; a custom dataset will not be provided. BioLINCC datasets generally contain only phenotypic data. Investigators interested in genotype and phenotype data from NHLBI funded studies should visit dbGaP.

If the researcher is unable to identify suitable resources through searching, a general Availability Request may be submitted from the Resource Overview or Studies dropdown page, and BioLINCC staff will assist.

3.3.2 REQUEST SUBMISSION

The request form will include the following components:

- **Request Identifier:** This is a nickname for the request.
- **Requestor Information:** Some fields are pre-populated from the information on the requestor's BioLINCC profile. The requestor should update their profile if information is missing or incorrect.
- **Support Information:** Information is requested regarding the requestor's institution, experience, and funding, if available.
- **Request Details:** The study to be requested automatically defaults to the study which was requested on its study webpage, but additional studies can be requested by clicking on the Study field under Request Details, which will bring a full list of available collections for multi-Study selection. The requestor is prompted for information on the study protocol or proposed research plan, whether the results will be used for a commercial purpose, and for the data security measures which will be utilized.
- **Attachments:** The requestor is asked to upload the required documentation (see Table 3.1) in PDF format. Optional documentation such as biographical sketch/curriculum vitae, abstract, and reference materials may also be uploaded.

3.3.3 REQUEST DOCUMENTATION

See Table 3.1

The study protocol can either be attached as a separate document (in PDF format) or described in the request form, and should include a brief overview of the requestor's research needs and design and analysis plan. The design and analysis plan may include participant inclusion/exclusion criteria, expected study visit periods, key analytic variables, primary and secondary outcome measure, follow-up period (if applicable), and intended statistical methods.

Institutional Review Board (IRB) or Ethics Committee (EC) documentation requirements include:

- PDF format
- Official institutional letterhead
- Name of the Principal Investigator
- Project title
- Notation of the approving committee/board
- An official stamp/seal, if applicable
- Level and determination of review (expedited, full, exempt)*
- Date of review determination
- Date of review expiration, if applicable
- The original document and a copy translated into English, if applicable, in the same format as the original and with the official's signature or seal/stamp and on institutional letterhead

*Some datasets require that the researcher's IRB provide full or expedited IRB/Ethics Committee review and approval of the proposed project. Such cases will be noted in the basic study information section of the Study Description Page (see section 2.4). In these cases, an IRB approval is needed because although obvious identifiers have been redacted, the wealth of individual level data that remain (demographic, anthropometric, medical history, personal history, outcomes) means that the possibility of direct identification of a study subject cannot be eliminated.

3.3.4 REQUEST REVIEW

BioLINCC staff will review the submitted request, and will notify the requestor via the comments tab if additional documentation or clarification is needed. If suitable to proceed, BioLINCC will formalize the request.

Once the required documentation is submitted and the request form is considered complete, BioLINCC staff will notify NHLBI staff to proceed with their review. The review includes:

- Appropriateness of the proposed research for the dataset(s) being requested
- Completion of the documentation requirements

NHLBI may have additional questions that BioLINCC will relay to the requestor via the comments tab.

3.3.5 REQUEST APPROVAL AND RMDA SIGNATURE

If NHLBI approves the request, the requestor will be directed to complete the required fields on the RMDA tab (see section 3.2.4) of their request. The fields on this form must be filled out before the Research Materials Distribution Agreement (RMDA) can be generated, however the requestor may reference the RMDA template for determining who should sign the RMDA. The template is for reference purposes only and should not be signed. The Principal Investigator and Authorized Institutional Business Official will be notified of their designation by email when the fields are completed or updated. Upon completion of this form, BioLINCC staff will review the information and request any changes if appropriate. It is important that these fields be filled in accurately. If after BioLINCC staff have generated the RMDA, the requestor finds that some of the information needs to be changed, they should update the fields on the RMDA tab so that BioLINCC staff may re-generate the RMDA with the corrected information.

Once BioLINCC generates the RMDA for the request, the Principal Investigator and Authorized Institutional Business Official will receive notifications from DocuSign with directions to complete and sign the agreement. Once completed, NHLBI will countersign and the fully signed copy will be uploaded to the RMDA tab. NHLBI will not sign an altered agreement.

Under the terms of the agreement:

1) Transferring data to any other institution or entity, including sites providing AI tools or resources, is not permitted.
2) A specific acknowledgement must be included in publications (see section 8 of the RMDA).
3) The use of the materials is restricted to the project proposed in the application. Any deviation or addition of a new project must be reviewed by NHLBI.
4) The Agreement must be renewed, or the data destroyed within one year.
5) Failure to adhere to the terms of the agreement will be taken into consideration by NHLBI for any future requests.

3.3.6 REQUEST COMPLETION

Once the RMDA is fully signed by all parties, BioLINCC staff will notify the requestor and authorize access to the data package. The datasets and associated documentation are posted in a package which may be accessed and downloaded via a secure link within the requestor's BioLINCC request. The data download link will be available for two weeks. The requestor will be notified of any updates to the data and given access to the data download link again, as long as the IRB and RMDA are not expired. The requestor is the only user that will be authorized to download BioLINCC datasets from the request.

3.4 STEPS FOR REQUESTING BIOSPECIMENS

3.4.1 SEARCH AND REGISTER

See section 3.3.1.

The requestor should verify on the Study Description Page (see section 2.4) that each study or studies being requested has biospecimens of interest under "Materials Available" and consult the tables in "Additional Details" for more detailed information regarding the study subjects and biospecimens included in the collection.

3.4.2 REQUEST SUBMISSION

Requestors are encouraged to be as specific as possible in their description of the search selection criteria, and to avoid the use of abbreviations and acronyms in their specifications. The request form will include the following components:

- **Request Identifier:** This is a nickname for the request.
- **Requestor Information:** Some fields are pre-populated from the information on the requestor's BioLINCC profile. The requestor should update their profile if information is missing or incorrect.
- **Support Information:** Information is requested regarding the requestor's institution, experience, and funding, if currently available. Biospecimen requests that do not have funding currently available should indicate anticipated primary funding source and application due date, accounting for any institutional or internal deadlines. Such requests may proceed with the biospecimen search (see section 3.4.4) but would then go on hold while funds are pursued. Requestors should submit the request at least three weeks in advance of their funding opportunity due date to allow sufficient time for the biospecimen search process.
- **Request Details:** The study to be requested automatically defaults to the study which was requested on its study webpage, but additional studies can be requested by clicking on the Study field under Request Details, which will bring a full list of available collections for multi-Study selection. The requestor is prompted for information on:
    - The study protocol or proposed research plan, including a summary of the rationale, main hypothesis and proposed research aims
    - Specimen requirements, such as anticoagulant used, additives, preservatives, etc.
    - Participant characteristics such as gender, age, disease status, etc.
    - Requested study visit(s) where the study or studies has biospecimens available from more than one visit, as detailed in the "Available Biospecimens" tables on each Study Description Page (see section 2.4)

- Number of participants and specimens, which may be different if multiple visits and/or material types are requested per participant
- Material type or types: note that availability of derived materials (such as DNA or RNA) that are not listed on the Study Description Page (see section 2.4) may be made available at NHLBI discretion
- Minimum/Optimum volume, or mass if requesting DNA or solid tissue
- Analyte(s) or parameter(s) to be tested
- Type of assay(s)/ platform(s) to be used
- Rationale for number of biospecimens requested, including power calculations, and describe the use of covariates, if applicable
- Whether the results will be used for a commercial purpose
- Whether the requestor was an investigator with the parent study or studies being requested

- **Attachments:** The requestor may upload any required or optional documentation (see Table 3.1), or documentation used to further specify any biospecimen search criteria. The requestor is encouraged to attach their documentation as early as possible in the request process. Any missing required documentation will be requested once the biospecimen search (see section 3.4.4) is completed.

3.4.3 PRELIMINARY REQUEST REVIEWS

BioLINCC staff will review the submitted request and will notify the requestor via the comments tab if clarification regarding the submitted criteria or other request form items is needed. The requestor may be asked to update the request form (see section 3.3.2) if information relayed in the comments is not reflected in the request form.

BioLINCC staff review the research plan against the informed consent document restrictions to ensure the research is acceptable. The requestor is notified immediately if the research plan is not acceptable and the biospecimen search cannot proceed. Restrictions vary by collection. For example, the consent may restrict the research to a specific disease area or for non-commercial research. Alternative biospecimen resources which do not have consent restrictions for the proposed research will be suggested if available.

A technical review is performed by Biorepository staff. The technical review determines if the selected biospecimens (including volume/concentration) are suitable for the proposed research protocol. Evidence that the proposed assays have been validated as sensitive enough and reproducible enough for the study is also considered. If the study itself is an assay validation, a pilot study using a subset of the requested biospecimens may be required.

3.4.4 BIOSPECIMEN SEARCH AND AVAILABILITY OF FUNDS

Once any questions are adequately answered, BioLINCC performs a search for suitable biospecimens based upon the information provided in the request. BioLINCC staff will identify

biospecimens meeting the requestor criteria and prepare an assessment of the availability and impact of the requested samples on the collection for NHLBI review. The elements taken into consideration in determining "impact" include historical use of the collection, the material type, volume remaining, potential for generating additional aliquots or expanding the material, and the availability of similar vials (i.e., the resource is not unique to the requested collection, and other lower-impact collections could be used).

BioLINCC will return the biospecimen search results to the requestor based on NHLBI determination of availability. The requestor may accept the results, ask for more information, or modify the criteria. If the criteria are modified, BioLINCC staff will update the availability assessment as needed and NHLBI will re-review.

BioLINCC staff will prepare a formal search summary that describes the search criteria and the numbers and characteristics of the biospecimens that were identified using these criteria, and the requestor will be notified to review the summary as a form within their BioLINCC request. The requestor will indicate whether the biospecimens identified are acceptable or not acceptable for the research.

If the request is not currently funded, the requestor may also request a letter of biospecimen availability for a funding opportunity on the search summary form. Access to the biospecimens described would be contingent upon scientific review by the funding group for the specific funding opportunity indicated on the request form. The request and biospecimens would be held for six months from the date on the letter of biospecimen availability, or until a decision is made regarding the funding for the application under the referenced funding opportunity, whichever is longer but not to exceed 12 months. If funding is obtained prior to the expiration date of the hold, the requestor is asked to notify BioLINCC immediately to ensure that the biospecimens remain available. Hold periods that expire without funding notification may not be extended. If the requestor's application is not funded, the requestor may pursue a re-application for the biospecimens by submitting a new BioLINCC request, where biospecimen availability will be re-assessed. This new request is required even if the proposed research has not changed.

Requestors should submit the request at least three weeks in advance of their funding opportunity due date to allow sufficient time for the biospecimen search process. If a biospecimen search is unable to be completed prior to the funding opportunity due date, BioLINCC staff can provide a letter stating that materials are available for request, but the biospecimens have not yet been identified as suitable and available for the proposed research.

Once funds are obtained or if funds are already available, BioLINCC will formalize the request and proceed with the next steps.

3.4.5 REQUEST DOCUMENTATION

See Table 3.1

BioLINCC staff will review any documentation already submitted and request any missing or inadequate documentation.

A comprehensive study protocol addresses all of the following topics:

- Summary of proposed research aims
- Analytes or parameters to be tested
- Type of assay(s)/platforms(s) to be used
- Scientific background and rationale
- Sample size rationale and calculations

The sample size justification should include the assumptions and approach used to calculate statistical power based on the biospecimen search results. Providing power results for several assumed or conjectured scenarios is a common approach for establishing and conveying the statistical power for a study. The requestor should provide enough detail to allow the power calculations to be reproduced by others who may be using different software. Formal calculations may not be necessary for a pilot study, however justification of the sample size should be addressed.

Institutional Review Board (IRB) or Ethics Committee (EC) documentation requirements include:

- PDF format
- Official institutional letterhead
- Name of the Principal Investigator
- Project title
- Notation of the approving committee/board
- An official stamp/seal, if applicable
- Level and determination of review (expedited, full, exempt)
- Date of review determination
- Date of review expiration, if applicable
- The original document and a copy translated into English, if applicable, in the same format as the original and with the official's signature or seal/stamp and on institutional letterhead

A few biospecimen collections are considered anonymized. That is, the link to the biospecimen has been destroyed and only limited data are available to investigators. Requestors of such biospecimen must follow their institutional guidelines regarding the use of anonymized biospecimens. If IRB approval/waiver is not consistent with the requestor's institutional guidelines for the use of anonymized biospecimens, other institutional documentation or policy statements should be substituted to document research compliance.

Documentation demonstrating that funds are available for this research may consist of a letter of award, or a letter of support, for example from the PI's department chair if institutional funds are being used.

3.4.6 FORMAL REQUEST REVIEWS

BioLINCC and Biorepository staff review the submitted documents for:

- The completeness of the request. The investigator is prompted for missing or incomplete documentation. If the submitted research protocol is determined to be incomplete, the investigator will be prompted to include the missing information before it will be sent onward for a scientific review.
- The suitability of the selected material types, volumes and proposed assay methods.
- The appropriateness of the number of biospecimens requested. For requests with a statistical analysis aspect, BioLINCC statistical staff will attempt to replicate the sample size and power calculations.

These reviews are designed to ensure that all the required documentation has been submitted, that the research protocol is technically feasible and the sample size is adequate to answer the research questions(s).

All requests for biospecimens undergo a scientific review. There are two review pathways:

- BioLINCC coordinates the scientific review of the proposed research plan. This is typically used when the applicant has existing funding to perform the proposed research.
- A funding group performs the scientific review of the proposed research plan. This is typically used when the applicant is searching for biospecimens prior to submitting an application to a funding group.

Scientific reviewers are asked to consider the following factors during their review:

- Significance of the Research Question
    - Does the project address an important problem or critical barrier to progress in the field?
    - If the goals of the project are achieved, will scientific knowledge, technical capability, and/or clinical practice be improved?
    - If the request is considered “High Impact” (i.e. the biospecimens are unique and limited):
        - Does the proposed research protocol warrant the use of valuable and limited biospecimens? [Note: “High Impact” requests require a corresponding “high impact” scientific question and outcome. Valuable biospecimens may not be used to perform exploratory research.]
        - Should this request be reviewed by external experts? Reviewers are asked to provide the names and contact information of external experts they consider appropriate for the request.
- Approach

    - Are the overall strategy, methodology, and analyses well-reasoned and appropriate to accomplish the project?
    - Are the BioLINCC and Biorepository reviews regarding suitability of biospecimens and sample size acceptable?
- Qualifications of the investigative team
    - Are the investigators qualified to perform the proposed research?

Upon completion of these reviews, BioLINCC staff will notify NHLBI staff to vote to approve, deny, or defer the request. The requestor is notified of the decision.

3.4.7 REQUEST APPROVAL, BIOSPECIMEN PROCESSING, AND RMDA SIGNATURE

If NHLBI approves the request, BioLINCC staff will work with the Biorepository to prepare the requested biospecimens for shipment. Note that the final vials for all requisitions are subject to visual inspection when retrieved from storage. Problem vials will be substituted with equivalent biospecimens wherever feasible, in consultation with the requestor.

A Research Materials Distribution Agreement (RMDA) must be completed prior to biospecimen shipment. The requestor will be directed to complete the required fields on the RMDA tab (see section 3.2.4) of their request. The fields on this form must be filled out before the RMDA can be generated, however the requestor may reference the RMDA template for determining who should sign the RMDA. The template is for reference purposes only and should not be signed. The Principal Investigator and Authorized Institutional Business Official will be notified of their designation by email when the fields are completed or updated. Upon completion of this form, BioLINCC staff will review the information and request any changes if appropriate. It is important that these fields be filled in accurately. If after BioLINCC staff have generated the RMDA, the requestor finds that some of the information needs to be changed, they should update the fields on the RMDA tab so that BioLINCC staff may re-generate the RMDA with the corrected information.

Once BioLINCC generates the RMDA for the request, the Principal Investigator and Authorized Institutional Business Official will receive notifications from DocuSign with directions to complete and sign the agreement. Once completed, NHLBI will countersign and the fully signed copy will be uploaded to the RMDA tab. NHLBI will not sign an altered agreement.

Under the terms of the agreement:

1) A specific acknowledgement must be included in publications (see section 8 of the RMDA).
2) The use of the materials is restricted to the project proposed in the application. Any deviation or addition of a new project must be reviewed by NHLBI.
3) Failure to adhere to the terms of the agreement will be taken into consideration by NHLBI for any future requests.

3.4.8 REQUEST COMPLETION

Once the RMDA is fully signed by all parties and the biospecimens have been shipped, BioLINCC will provide the study data and linking file(s) to associate the biospecimens with the data (if requested and applicable). The vial level biospecimen data will be included on electronic manifests provided by the NHLBI Biorepository at the time of shipment, via email.

3.5 APPROVED USERS AND COLLABORATORS

The RMDA holds the Principal Investigator and the signing recipient institution responsible for adhering to the terms of the agreement, including maintaining BioLINCC materials in a secure manner. The Principal Investigator (PI) is responsible for oversight of Approved Users of BioLINCC materials, and the PI may add additional Approved Users within his/her institution at his/her discretion.

If the project involves collaborators from an outside institution, the collaborators must submit and complete a separate BioLINCC request prior to accessing any BioLINCC data and/or biospecimens. For biospecimens, the use of testing labs outside of the recipient institution is in compliance with the terms of the RMDA as long as the lab is under a contractual non-disclosure agreement such that the biospecimens remain within the purview of the Principal Investigator and his/her institution.

3.6 AFTER REQUEST FULFILLMENT

3.6.1 PROGRESS REPORTS

Email notifications requesting a Progress Report for the project described in a fulfilled request are sent annually. Requestors may also submit a Progress Report via their request page at any point after receipt of materials. The Progress Report allows requestors to submit information regarding the overall progress of the project, any abstracts or manuscripts that have been submitted or published, whether the project has been completed, and if completed, whether the data have destroyed per the terms of the Research Materials Distribution Agreement (RMDA) (see section 3.6.3). Publication references resulting from the use of BioLINCC materials may be displayed in the Publications section of the BioLINCC website.

3.6.2 CHANGES TO THE APPROVED RESEARCH PLAN

Minor changes to the proposed project (changes in exclusion/inclusion criteria, follow-up length, covariates, general analytic approach, etc.) without a change in the research aims or hypothesis do not require additional review by NHLBI. Substantial changes in the project (different outcome, additional research aims, etc.) would require that the requestor submit a new protocol/description of the research which will be sent to NHLBI to review as an additional project or project revision. The updated protocol may be submitted on the comments page of the relevant BioLINCC request or by email to biolincc@imsweb.com.

3.6.3 RMDA EXPIRATION, DATA DESTRUCTION, AND RENEWAL REQUESTS

The RMDA completed for any request involving study dataset is valid for one year from NHLBI signature. BioLINCC staff will send reminders when the agreement is nearing expiration with instructions to renew access or destroy the data. A renewal request requires both a progress report and submission of current IRB documentation, which may take the form of the most recent continuing review from the IRB, or submission of a new protocol if continuing reviews have lapsed. Exemptions are also accepted unless otherwise noted in a study's description. Requestors that complete a Renewal Request will also be eligible to receive any updates made to the data.

If the project has been completed or the RMDA has expired with no intent to renew, the requestor must complete the Certificate of Destruction and submit it and a report on current progress to BioLINCC via the progress report form or by email to biolincc@imsweb.com. As stated in section 11 of the RMDA, failure to adhere to the terms of the RMDA will be taken into consideration with respect to any future requests for data and/or biospecimens from the NHLBI repositories.

Renewal requests are not applicable if the Principal Investigator of the project has changed or if the project is moving to a new institution. In such cases, an entirely new data and/or biospecimen (as applicable) request must be submitted and completed. Transfer of BioLINCC data to a new institution requires confirmation that any data remaining at the previous institution have been destroyed, or transferred to a new Principal Investigator under a new RMDA.

The RMDA for biospecimen-only requests does not expire and renewals are not required.